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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,955	07/07/2003	Hirohiko Tsuzuki	Q76105	4760

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EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 03/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,955	TSUZUKI ET AL.	
	Examiner	Art Unit	
	Satyendra K. Singh	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendments to the claims filed with the office on December 7th 2005 is duly acknowledged.

Claims 1-19 are pending in the application.

Claims 1-11 and 16 are withdrawn from further consideration.

Claim 20 has been cancelled by applicant's present amendment to the claims.

Claims 12-15 and 17-19 are being currently examined on their merits, herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Hara et al (U.S. Patent 6,821,107 B1, [A]).

Claim 18 is drawn to **a cell culture (product)** obtained by the method according to claim 17 that uses the carrier for cell culture as claimed in claim 12.

As per MPEP § 2113 *"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a*

different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Hara et al [A] teaches such a cell culture (a layer of fibroblast cells cultured on a cell culture carrier comprising an alginate gel layer coated with collagen) obtained by the method for culturing cells (see Hara et al, column 7-8, example 2-3, in particular) which are the same as claimed in the instant invention irrespective of the changes in the carrier for cell culture made in the present application. The presence of chitosan layer in between collagen and alginate gel layers may provide added benefits (such as extra reinforcement, etc.) for lamination and other related procedures, but will not significantly change the cultured product as claimed.

Response to Applicant's Arguments

Claim 18 remains rejected under 35 U.S.C. 102(b) as being anticipated by Hara et al (U.S. Patent 6,821,107 B1, [A]). Claim is drawn to a "cell culture" (a product by process) obtained by the method of claim 17 that uses the carrier for cell culture according to claim 12 (see instant claims 12, and 17). Applicant's arguments (see applicant's remarks, page 5 and 6, in particular) have been fully considered but were not found to be persuasive. Applicants argue that "while the patentability of a product-by-process claim is based upon the product itself, the examiner is not free to disregard clear **structural distinctions** between the product of the art and the claimed product (MPEP § 2111), and since the Hara et al does not teach a chitosan layer in the carrier for cell culture, the rejection on its face is a legally improper §102(b) rejection".

Applicants are reminded that the limitation of the instant claim 18 as presented, does not require the "carrier for cell culture" to be present along with the cultured product (cell culture), and therefore, the cell culture product obtained by the method of Hara et al using their carrier for cell culture, is deemed to anticipate the product obtained by the method of instant claim 17 using the carrier according to claim 12. In the absence of any other disclosure provided by applicants in the instant specification regarding the patentability of a "distinct cell culture product" obtained by the method of claim 17, the product obtained by the method of Hara et al is deemed to anticipate the invention of claim 18, as set forth in the previous office action (see also discussion, supra). As stated supra, the presence of chitosan layer in the carrier for cell culture of the instant invention, may provide added benefit (in terms of reinforcement, etc.) for lamination and other cell culture related procedures, but will not significantly change the cultured product obtained from the method as claimed. Thus, the rejection under §102(b) is deemed proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12-15 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al (U.S. Patent 6,821,107 B1, [A]) in view of Huguet & Dellacherie [U] and Clapper et al (U.S. Patent 5,512,474 [B]).

Linking claims 12-15 are drawn to a carrier for cell culture that comprises a water-containing gel comprising alginate or alginate/polylysine, wherein a surface of the carrier is coated with collagen, and wherein the collagen and the water-containing gel containing alginate are intermediated by a layer of chitosan, and wherein the alginate containing carrier for cell culture is formed on a porous membrane.

The carrier for cell culture, as claimed in the present invention, is formed on a porous membrane and comprises of a layer of alginate gel coated with collagen containing an intermediate layer of chitosan between alginate gel layer and collagen coating, and may enable culture (as well as visualization) of mammalian cells (anchorage-dependent or adherent cultures) on the collagen layer using various culture media and conditions used for standard cell culture.

Claims 17-19 are drawn to a method for culturing cells and a cell culture obtained by such method using the carrier for cell culture as claimed in claim 12.

Hara et al [A] teach a carrier for cell culture comprising an alginate gel layer (calcium alginate as claimed in the instant claim 13) formed on a porous membrane (as claimed in the instant claim 15) having an extracellular matrix component gel layer

(made of collagen) or extracellular matrix component sponge layer formed on the alginate gel layer (see Hara et al, abstract, fig. 1 and 2, summary of the invention, and example 1, in particular). Hara et al [A] also teach a method for culturing cells, a method for producing cell culture, and a cell culture obtained by the methods using the carrier for cell culture where the cell layer is formed on the extracellular matrix component gel layer or extracellular matrix component sponge layer or on the alginate gel layer by the method step of allowing the cells to grow and form a cell layer on the surface of the carrier for cell culture (see Hara et al, example 2, in particular). In addition, the alginate gel layer is solubilized using chelating agent to exfoliate cell layer from the porous membrane, and the exfoliated cell layer is further laminated on another cell layer on a carrier providing a method of forming a structure having multiple cell layers (see Hara et al, abstract, fig 1 & 2, summary, and examples 2-3, in particular).

However, a carrier for cell culture wherein the collagen layer is bound to a surface of the water-containing gel (comprising alginate) by means of **chitosan as an intermediate layer** is not taught by Hara et al [A].

Huguet & Dellacherie [U] teach a microcapsule (suitable for microencapsulation of biological materials, including cells) comprising calcium alginate beads that are coated with chitosan as an outermost layer in order to study the rate of release of biological materials such as proteins, and dextran (having different molecular weights) from the encapsulated beads (see Huguet & Dellacherie, abstract, introduction, methods, pages 745-746, in particular and references therein).

In addition, Clapper et al [B] teach a cell culture system comprising a support material providing a surface for the attachment of cells (for the purpose of anchorage-dependent cell culture) comprising a stable combination of positively charged molecule (chitosan) and cell adhesion factor (collagen) (see Clapper et al, abstract, summary, column 3-4, in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the carrier for cell culture of Hara et al [A] (and therefore, the methods steps for culturing and producing the cell culture using such modified carrier) comprising an alginate gel layer formed on a porous membrane which is further coated with a collagen layer, such that the collagen gel layer is bound to a surface of alginate by means of a polycationic polysaccharide (such as chitosan) as explicitly taught by Huguet & Dellacherie [U] and Clapper et al [B].

The person of ordinary skill in the art would have been motivated to make that modification in the carrier for cell culture (and therefore, the methods steps dependent on it) by incorporating an intermediate layer containing chitosan (which is bound to the layers of collagen and water-containing gel containing alginate) because -1) Huguet & Dellacherie disclose the benefits of coating calcium alginate with chitosan in order to providing strength and reinforcement to the water-containing gel (alginate gel) layer (see Huguet & Dellacherie, page 745, abstract and introduction, in particular); and -2) Clapper et al [B] explicitly disclose the benefits of using polycationic or positively charged molecule (chitosan or polylysine) in combination with cell adhesion factor (collagen, etc.) bound to the surface of a cell culture support of a bioreactor to improve

cell attachment and stabilize cell growth (see Clapper et al, abstract, summary, and column 3-4, and examples, in particular).

One of ordinary skill in the art would have had a reasonable expectation of success when modifying the carrier for cell culture (and therefore, the attendant method steps using such modified carrier for cell culture) as taught by Hara et al by incorporating an intermediate layer of chitosan (between the layers of water-containing alginate gel and collagen) as taught by Huguet & Dellacherie and Clapper et al because the prior arts explicitly teach the method steps involved in the preparation and use of chitosan for coating the alginate gel layer as well as the method for the providing coating of chitosan and collagen on a cell culture support system for obtaining enhanced cell attachment in anchorage-dependent cell culture systems.

Although, the shape of the cell culture carriers taught by both Huguet & Dellacherie and Clapper et al are different than the instant invention, the method steps required to form layers of collagen and chitosan are same, and therefore, are immaterial to the benefits associated with such modification in the carrier for cell culture (as taught by Hara et al) using chitosan as an intermediate layer between alginate gel layer and collagen layer.

Since the benefits accruing from such a modification would provide an effective, biocompatible, reinforced support system for use in cell culture methods for mammalian cells that may require transfer of the cell culture product, lamination of the cultured cell layers, and formation of multilayered cell structures resulting in three-dimensional tissue structures (as disclosed by Hara et al, see column 7, first paragraph, in particular), one

of ordinary skill in the art would be motivated to combine the teachings of the Huguet & Dellacherie and Clapper et al with the teachings of Hara et al to modify their carrier for cell culture (and hence the methods using that carrier) as claimed in the present invention.

As per MPEP, *"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945)"* (see MPEP 2144.07).

Thus, the invention as a whole would have been *prima facie* obvious to one skilled in the art at the time the claimed invention was made.

Response to Applicant's Arguments

Claims 12-15 and 17-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al (U.S. Patent 6,821,107 B1, [A]) in view of Huguet & Dellacherie [U] and Clapper et al (U.S. Patent 5,512,474 [B]). Applicant's arguments (see applicant's remarks, page 7 and 8, in particular) were fully considered but were not found to be persuasive. Applicants argue that Hara et al does not teach a cell culture carrier containing an intermediate layer of chitosan in the form of a sheet, to reinforce the said carrier, nor does it suggest that further support or enhancement of cell attachment would be needed or would be otherwise beneficial. Applicants further argue that Huguet & Dellacherie teach a microcapsule containing chitosan as a core substance, and do not teach or suggest that chitosan can be used in the form of a sheet or layer to reinforce a water containing gel layer in order to confer unexpected advantages such as transparency, permeability, etc.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., structural limitations such as cell culture carrier support layers in the form of a sheet, etc.) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the invention of Hara et al teach a cell culture carrier comprising water containing gel layer (such as alginate layer) formed on a porous support membrane that is coated with extracellular matrix component (such as collagen), the inventions of Huguet & Dellacherie and Clapper et al provide the disclosures that water containing alginate beads can be reinforced with chitosan as an outermost layer as well as the fact that chitosan gel can be combined with an extracellular matrix material such as collagen to obtain a cell culture carrier with superior qualities for the attachment and stabilization of cells and cell growth. As discussed supra, though, the shape of the cell culture carriers taught by both Huguet & Dellacherie and Clapper et al are different than the instant invention, the

components and the method steps required to form layers of collagen and chitosan are same, and therefore, are immaterial to the benefits associated with such modification in the carrier for cell culture (as taught by Hara et al) using chitosan as an intermediate layer between alginate gel layer and collagen layer, and therefore, would effectively provide the same benefits associated with the use of chitosan layer (such as transparency, permeability, etc.) as argued by the applicants. Therefore, the obviousness rejections as set forth under 35 U.S.C. 103(a) in the previous office action are maintained over the cited prior arts.

Conclusion

No claims are allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyendra K. Singh whose telephone number is 571-272-8790. The examiner can normally be reached on 9-5MF (with alternate Fridays OFF).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyendra K. Singh
Patent Examiner
Art Unit 1651

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PRIMARY EXAMINER